REMARKS

Claim status. Claims 1 to 7, 9 to 11, 22 to 25, and 52 are pending in this application. Claims 7, 9, 11, and 22 to 25 are withdrawn from consideration. All remaining claims (1 to 6, 10, and 52) stand rejected under 35 U.S.C. Section 103. Claims 9, 11, and 22 to 25 are canceled hereby. No claim has been added or amended.

Support for Amendments. The amendment to page 1 merely adds the cross-reference, which was previously requested in the Transmittal Letter. The amendments to the Sequence Listing merely add the feature information requested in the Notice to Comply in a related application. All of such information added to the Sequence Listing was taken from the specification. The remaining amendments to the specification correct the sequence numbering. Thus, the amendments are supported in the specification as originally filed and no new matter is added to the specification.

Rejections under Section 103(a). Claims 1 to 6 stand rejected over WO 98/24477 (Bendele *et al.*) or WO 97/28828 (Collins *et al.*) alone or in view of WO 99/142/44 (Kohler). Claims 1 to 6, 10, and 52 were rejected over Bendele *et al.* or Collins *et al.* in view of Kohler, U.S. Pat. No. 5,608,035 (Yanofsky *et al.*), and WO 98/46257 (Brems *et al.*).

The rejection under Section 103(a) fails to supply any suggestion for the desirability of the combination and the references, even in combination, do not comprise the claimed invention.

The Bendele *et al.* reference is directed toward combination therapy using an IL-1 inhibitor and an additional anti-inflammatory drug, such as methotrexate. The Collins *et al.* reference is directed toward a composition comprising an IL-1 inhibitor and a controlled release polymer. The Office Action cites both the Bendele and Collins references for teaching "a carboxy-terminus modified chimeric protein which is a fusion of IL-1ra and 'all or part of the constant domain of the heavy or light chain of human immunoglobulin.' " (Office Action at page 3). The Office Action states, "This reads on applicants' invention when c=0. They [sic] only difference between the claimed invention and the references is that the references do not specifically make the suggested chimeric protein and that the claims encompasses [sic] the use of a linker...."

The Collins and Bendele references discuss the protein known as IL-1ra but they do not suggest fusion between an Fc domain and a peptide. The relevant sequences provided in the specification are of IL-1 inhibitory peptides, not proteins or protein fragments, and the peptides do not have sequence identity with IL-1ra or soluble IL-1 receptor. Neither the Bendele nor the Collins reference suggests combination of an Fc domain with an IL-1 inhibitory peptide.

The Brems *et al.* reference concerns conjugates of ob protein with Fc. It does not disclose fusion of Fc with peptides of any kind.

The Kohler reference concerns a method of cross-linking biologically active, immunogenic peptides to antibodies. Thus, the molecules envisioned by Kohler comprise full antibodies--full-length heavy and light chains--

with the addition of immunogenic peptides. These molecules differ significantly from the claimed molecules having one or more peptides linked to an Fc domain. More important, the Office Action does not make clear how Kohler is actually applicable as prior art. Kohler was filed prior to the American Inventors Protection Act, published after the Applicants' priority date, and the Office Action does not clarify under what statutory authority Kohler qualifies as prior art. The Applicants request clarification on which section of 35 U.S.C. would make Kohler prior art to the subject application.

The Yanofsky *et al.* reference concerns peptides that bind to the IL-1 receptor. The Yanofsky reference notes that its peptides can serve as structural models for non-peptidic compounds (col. 20, lines 61 to 67), which substantially agrees with the Applicants' statement at page 10, lines 2 to 13. The Yanofsky reference describes *in vivo* uses, pharmaceutical compositions, dosage, and dosage forms (col. 22, line 11 to col. 24, line 32). The Yanofsky reference, does not, however, recognize the desirability of increasing the half-life of such peptides (*Cf.* specification at page 10, lines 15 to 17; page 17, lines 15 to 25) and does not further suggest accomplishing such-increased half-life by linkage to an Fc domain.

None of the references suggest the desirability of their combination, nor the desirability of combining peptides with an Fc domain. Only the Yanofsky and Kohler references concern peptides, and they show no recognition of the desirability of half-life extension by Fc linkage. The other cited references, like the references included in the specification in Table 1 at page 2, all refer to proteins. Furthermore, the first patent describing Fc fusion refers to fusion with "*protein* known to function to bind specifically to target ligand molecules, and are generally found in their native state as secreted or membrane bound polypeptides...." (U.S. Pat. No. 5,428,130, Reference A6, at Col. 7, lines 15-21, emphasis added). Other than the Applicants' invention, the first suggestion regarding Fc linkage to peptides came after the Applicants' filing date in WO 01/02440 A1 (Reference B13), which does not qualify as prior art.

The Applicants also would like to call the Examiner's attention to aspects of particular claims.

Regarding Claim 4, the claim requires that more than one peptide be included in tandem, separated by an optional linker, in the fusion molecule with the Fc domain. The Bendele, Collins, and Brems references all concern a single protein linked to the Fc, with no suggestion of multiple proteins (let alone peptides) fused to the Fc. The Kohler reference, as noted above, concerns cross-linking derivatives of peptides to full antibodies by a photochemical reaction. Thus, in addition to the differences noted above, the multiple peptide aspect of claim 4 provides an additional reason for patentability.

Regarding Claim 7, the Applicants note that the sequence recited therein concerns the Fc domain rather than the peptide portion of the claimed molecule. A search regarding Claim 7 would substantially overlap any search regarding Fc-linked molecules, as both would substantially involve the Fc sequence. Thus, the Applicants respectfully request that Claim 7 remain in the present application.

Conclusion. In light of the foregoing, the Applicants respectfully request entry of all amendments and allowance of all claims.

Respectfully submitted,

Timothy J. Gaul
Attorney for Applicants
Registration No.: 33,111
Phone: (805) 447-2688
Date: February 28, 2002

Please send all future correspondence to:

US Patent Operations/ TJG
Dept. 4300, M/S 27-4-A
AMGEN INC.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

VERSION WITH MARKINGS TO SHOW CHANGES MADE

At page 1, line 1:

Cross-Reference to Related Applications

This applications claims the benefit of United States Provisional application 60/105,371, filed October 23, 1998.

At page 58, Table 20:

Table 20—Additional Exemplary Pharmacologically Active Peptides

Sequence/structure	SEQ ID NO:	Activity
VEPNCDIHVMWEWECFERL	1027	VEGF-antagonist
GERWCFDGPLTWVCGEES	~~1084~~ 398	VEGF-antagonist
RGWVEICVADDNGMCVTEAQ	1085	VEGF-antagonist
GWDECDVARMWEWECFAGV	1086	VEGF- antagonist
GERWCFDGPRAWVCGWEI	501	VEGF- antagonist
EELWCFDGPRAWVCGYVK	502	VEGF- antagonist
RGWVEICAADDYGRCLTEAQ	1031	VEGF- antagonist
RGWVEICESDVWGRCL	1087	VEGF- antagonist
RGWVEICESDVWGRCL	1088	VEGF- antagonist
GGNECDIARMWEWECFERL	1089	VEGF- antagonist
RGWVEICAADDYGRCL	1090	VEGF-antagonist
CTTHWGFTLC	1028	MMP inhibitor
CLRSGXGC	1091	MMP inhibitor
CXXHWGFXXC	1092	MMP inhibitor
CXPXC	1093	MMP inhibitor
CRRHWGFEFC	1094	MMP inhibitor
STTHWGFTLS	1095	MMP inhibitor
CSLHWGFWWC	1096	CTLA4-mimetic
GFVCSGIFAVGVGRC	125	CTLA4-mimetic
APGVRLGCAVLGRYC	126	CTLA4-mimetic
LLGRMK	105	Antiviral (HBV)
ICVVQDWGHHRCTAGHMANLTSHASAI	127	C3b antagonist
ICVVQDWGHHRCT	128	C3b antagonist
CVVQDWGHHAC	129	C3b antagonist
STGGFDDVYDWARGVSSALTTTLVATR	185	Vinculin-binding
STGGFDDVYDWARRVSSALTTTLVATR	186	Vinculin-binding
SRGVNFSEWLYDMSAAMKEASNVFPSRRSR	187	Vinculin-binding
SSQNWDMEAGVEDLTAAMLGLLSTIHSSSR	188	Vinculin-binding
SSPSLYTQFLVNYESAATRIQDLLIASRPSR	189	Vinculin-binding
SSTGWVDLLGALQRAADATRTSIPPSLQNSR	190	Vinculin-binding
DVYTKKELIECARRVSEK	191	Vinculin-binding
EKGSYYPGSGIAQFHIDYNNVS	192	C4BP-binding

SGIAQFHIDYNNVSSAEGWHVN	193	C4BP-binding
LVTVEKGSYYPGSGIAQFHIDYNNVSSAEGWHVN	194	C4BP-binding
SGIAQFHIDYNNVS	195	C4BP-binding
LLGRMK	279	anti-HBV
ALLGRMKG	280	anti-HBV
LDPAFR	281	anti-HBV
CXXRGDC	322	Inhibition of platelet aggregation
RPLPPLP	323	Src antagonist
PPVPPR	324	Src antagonist
XFXDXWXXLXX	325	Anti-cancer (particularly for sarcomas)
KACRRLFGPVDSEQLSRDCD	326	p16-mimetic
RERWNFDFVTETPLEGDFAW	327	p16-mimetic
KRRQTSMTDFYHSKRRLIFS	328	p16-mimetic
TSMTDFYHSKRRLIFSKRKP	329	p16-mimetic
RRLIF	330	p16-mimetic
KRRQTSATDFYHSKRRLIFSRQIKIWFQNRRMKWKK	331	p16-mimetic
KRRLIFSKRQIKIWFQNRRMKWKK	332	p16-mimetic
Asn Gln Gly Arg His Phe Cys Gly Gly Ala Leu Ile His Ala Arg Phe Val Met Thr Ala Ala Ser Cys Phe Gln	498	CAP37 mimetic/LPS binding
Arg His Phe Cys Gly Gly Ala Leu Ile His Ala Arg Phe Val Met Thr Ala Ala Ser Cys	499	CAP37 mimetic/LPS binding
Gly Thr Arg Cys Gln Val Ala Gly Trp Gly Ser Gln Arg Ser Gly Gly Arg Leu Ser Arg Phe Pro Arg Phe Val Asn Val	500	CAP37 mimetic/LPS binding
WHWRHRIPLQLAAGR	1097	carbohydrate (GD1 alpha) mimetic
LKTPRV	1098	β2GPI Ab binding
NTLKTPRV	1099	β2GPI Ab binding
NTLKTPRVGGC	1100	β2GPI Ab binding
KDKATF	1101	β2GPI Ab binding
KDKATFGCHD	1102	β2GPI Ab binding
KDKATFGCHDGC	1103	β2GPI Ab binding
TLRVYK	1104	β2GPI Ab binding
ATLRVYKGG	1105	β2GPI Ab binding
CATLRVYKGG	1106	β2GPI Ab binding
INLKALAALAKKIL	1107	Membrane-transporting
GWT	NR	Membrane-transporting
GWTLNSAGYLLG	1108	Membrane-transporting
GWTLNSAGYLLGKINLKALAALAKKIL	1109	Membrane-transporting

At page 109, lines 3-15:

The Fc portion of the molecule was generated in a PCR reaction with pFc-A3 using the primers

1216-52 AAC ATA AGT ACC TGT AGG ATC G

1798-17 AGA GTA AGT ACC TCC ACC ACC ACC TCC ACC TTT ACC CGG
AGA CAG GGA GAG GCT CTT CTG C

which are SEQ ID NOS: ~~398~~369 and 399, respectively. The oligonucleotides 1798-17 and 1798-18 contain an overlap of 61 nucleotides, allowing the two genes to be fused together in the correct reading frame by combining the above PCR products in a third reaction using the outside primers, 1216-52 and 1798-19.

At page 113, lines 22-23:

The nucleotide and amino acid sequences (SEQ ID NOS: ~~—~~21 and ~~—~~22, respectively) of the fusion protein are shown in Figure 16.

At page 114, lines 20-30 and page 115, lines 1-5:

Fc-TNF-α inhibitors. A DNA sequence coding for the Fc region of human IgG1 fused in-frame to a monomer of the TNF-α inhibitory peptide was constructed using standard PCR technology. The Fc and 5 glycine linker portion of the molecule was generated in a PCR reaction with DNA from the Fc-EMP fusion strain #3718 (see Example 3) using the sense primer 1216-52 and the antisense primer 2295-89 (SEQ ID NOS: ~~1112~~369 and ~~1113~~1112 , respectively). The nucleotides encoding the TNF-α inhibitory peptide were provided by the PCR primer 2295-89 shown below:

1216-52 AAC ATA AGT ACC TGT AGG ATC G

2295-90 CCG CGG ATC CAT TAC GGA CGG TGA CCC AGA GAG GTG TTT TTG TAG
TGC GGC AGG AAG TCA CCA CCA CCT CCA CCT TTA CCC

The oligonucleotide 2295-89 overlaps the glycine linker and Fc portion of the template by 22 nucleotides, with the PCR resulting in the two genes being fused together in the correct reading frame.

At page 117, lines 21-30 and page 118, lines 1-8:

Fc-IL-1 antagonist. A DNA sequence coding for the Fc region of human IgG1 fused in-frame to a monomer of an IL-1 antagonist peptide was constructed using standard PCR technology. The Fc and 5 glycine linker portion of the molecule was generated in a PCR reaction with DNA from the Fc-EMP fusion strain #3718 (see Example 3) using the sense primer 1216-52 and the antisense primer 2269-70 (SEQ ID NOS: ~~1112~~369 and 1118, respectively). The nucleotides encoding the IL-1 antagonist peptide were provided by the PCR primer 2269-70 shown below:

1216-52 AAC ATA AGT ACC TGT AGG ATC G

2269-70 CCG CGG ATC CAT TAC AGC GGC AGA GCG TAC GGC TGC CAG TAA CCC GGG GTC CAT TCG AAA CCA CCA CCT CCA CCT TTA CCC

The oligonucleotide 2269-70 overlaps the glycine linker and Fc portion of the template by 22 nucleotides, with the PCR resulting in the two genes being fused together in the correct reading frame.

At page 121, lines 4-15:

Fc-VEGF Antagonist. A DNA sequence coding for the Fc region of human IgG1 fused in-frame to a monomer of the VEGF mimetic peptide was constructed using standard PCR technology. The templates for the PCR reaction were the pFc-A3 plasmid and a synthetic VEGF mimetic peptide gene. The synthetic gene was assembled by annealing the following two oligonucleotides primer (SEQ ID NOS: ~~1120~~1110 and ~~1121~~1111, respectively):

2293-12 GTT GAA CCG AAC TGT GAC ATC CAT GTT ATG TGG GAA TGG GAA TGT TTT GAA CGT CTG

2293-13 CAG ACG TTC AAA ACA TTC CCA TTC CCA CAT AAC ATG GAT GTC ACA GTT CGG TTC AAC

At page 121, lines 17-18:

The two oligonucleotides anneal to form the following duplex encoding an amino acid sequence shown below (SEQ ID NOS: ~~1122~~1113 and 1114):

At page 121, lines 28-29:

This duplex was amplified in a PCR reaction using 2293-05 and 2293-06 as the sense and antisense primers (SEQ ID NOS: ~~1125~~1122 and ~~1126~~1123).

At page 121, lines 30-34::

The Fc portion of the molecule was generated in a PCR reaction with the pFc-A3 plasmid using the primers 2293-03 and 2293-04 as the sense and antisense primers (SEQ ID NOS: ~~1123~~1120 and ~~1124~~1121, respectively). The full length fusion gene was obtained from a third PCR reaction using the outside primers 2293-03 and 2293-06. These primers are shown below:

At page 122, lines 22-31::

VEGF antagonist -Fc. A DNA sequence coding for a VEGF mimetic peptide fused in-frame to the Fc region of human IgG1 was constructed using standard PCR technology. The templates for the PCR reaction were the pFc-A3 plasmid and the synthetic VEGF mimetic peptide gene described above. The synthetic duplex was amplified in a PCR reaction using 2293-07 and 2293-08 as the sense and antisense primers (SEQ ID NOS: ~~1127~~1124 and ~~1128~~1125, respectively).

The Fc portion of the molecule was generated in a PCR reaction with the pFc-A3 plasmid using the primers 2293-09 and 2293-10 as the sense and antisense primers (SEQ ID NOS: ~~1129~~1126 and ~~1130~~1127, respectively).

At page 123, lines 27-32 and page 124, lines 1-22:

Fc-MMP inhibitor. A DNA sequence coding for the Fc region of human IgG1 fused in-frame to a monomer of an MMP inhibitory peptide was constructed using standard PCR technology. The Fc and 5 glycine linker portion of the molecule was generated in a PCR reaction with DNA from the Fc-TNF-α inhibitor fusion strain #4544 (see Example 4) using the sense primer 1216-52 and the antisense primer 2308-67 (SEQ ID NOS: ~~1112~~369 and ~~1131~~1115, respectively). The nucleotides encoding the MMP inhibitor peptide were provided by the PCR primer 2308-67 shown below:

1216-52 AAC ATA AGT ACC TGT AGG ATC G

2308-67 CCG CGG ATC CAT TAG CAC AGG GTG AAA CCC CAG TGG GTG GTG CAA CCA CCA CCT CCA CCT TTA CCC

The oligonucleotide 2308-67 overlaps the glycine linker and Fc portion of the template by 22 nucleotides, with the PCR resulting in the two genes being fused together in the correct reading frame.

At page 124, replace this paragraph, lines 22-35, with the following:

MMP Inhibitor-Fc. A DNA sequence coding for an MMP inhibitory peptide fused in-frame to the Fc region of human IgG1 was constructed using standard PCR technology. The Fc and 5 glycine linker portion of the molecule was generated in a PCR reaction with DNA from the Fc-TNF-α inhibitor fusion strain #4543 (see Example 4). The nucleotides encoding the MMP inhibitory peptide were provided by the sense PCR primer 2308-66, with primer 1200-54 serving as the antisense primer (SEQ ID NOS: ~~1132~~1116 and 407, respectively). The primer sequences are shown below:

2308-66 GAA TAA CAT ATG TGC ACC ACC CAC TGG GGT TTC ACC CTG TGC GGT GGA GGC GGT GGG GAC AAA

1200-54 GTT ATT GCT CAG CGG TGG CA